CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074729

Trade Name : TOLMETIN SODIUM TABLETS 600MG

Generic Name: Tolmetin Sodium Tablets USP 600mg

Sponsor : Lemmon Company

Approval Date:February 27, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074729

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074729

APPROVAL LETTER

ANDA 74-729

FEB 27 1997

Lemmon Company
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

Dear Madam:

This is in reference to your abbreviated new drug application dated August 11, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Tolmetin Sodium Tablets USP, 600 mg (base).

Reference is also made to your amendments dated August 5, 1996 and February 5, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Tolmetin Sodium Tablets USP 600 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Tolectin® 600 mg Tablet; R W Johnson Pharmaceutical Research Institute). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-729
Division File
Field Copy
HFD-600/Reading File
HFD-92
HFD-8/P.Savino
HFD-610/J.Phillips

Endorsements:

HFD-623/M.Maust/2-13-97
HFD-623/V.Sayeed, Ph.D./2-14-97
HFD-617/J.Wilson, P.M./2-18-97
HFD-620/A.Rudman, Ph.D./
HFD-613/C. Park/
X:\NEW\FIRMSAM\[illegible]
F/T by: bc/2-19-97

APPROVE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074729

FINAL PRINTED LABELING

NDC 0093-0214-01

TOLMETIN SODIUM Tablets, USP

600 mg*

Caution: Federal law prohibits dispensing without prescription.

100 TABLETS

LEMMON

* Each tablet contains Tolmetin Sodium USP, 735 mg equivalent to 600 mg of Tolmetin.

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

This is a bulk container. Not intended for household use.

Protect from light.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TP Rev. A 4/96

Manufactured by:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Distributed by:
LEMMON COMPANY
Sellersville, PA 18960

0093-0214-01

FEB 27

APPROVED

NDC 0093-0214-10

TOLMETIN SODIUM Tablets, USP

600 mg*

Caution: Federal law prohibits dispensing without prescription.

APPROVED

1000 TABLETS

LEMMON

* Each tablet contains Tolmetin Sodium USP, 735 mg equivalent to 600 mg of Tolmetin.

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

This is a bulk container. Not intended for household use.

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0093-0214-10

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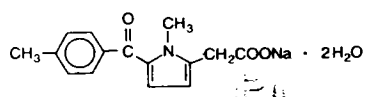
0214 # TOLMETIN SODIUM TABLETS, USP

DESCRIPTION
Each tablet, for oral administration, contains 735 mg of tolmetin sodium (as the dihydrate), equivalent to 600 mg of tolmetin. Each tablet contains 54 mg (2.35 mEq) of sodium. In addition, each tablet contains the following inactive ingredients: Carmine BPC, Colloidal Silicon Dioxide, Crospovidone, D & C Yellow No. 10 (Aluminum Lake), FD&C Yellow No. 6 (Aluminum Lake), Hydroxypropyl Methylcellulose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol 400, Corn Starch, and Titanium Dioxide.

Tolmetin sodium is a nonsteroidal anti-inflammatory agent. Chemically it is Sodium 1-methyl-5-*p*-toluoylpyrrole-2-acetate dihydrate. The structural formula is:



$C_{15}H_{14}NNaO_3 \cdot 2H_2O$ M.W. 315.30

Tolmetin sodium is a light yellow to light orange, crystalline powder. It is freely soluble in water. The pKa of tolmetin is 3.5.

CLINICAL PHARMACOLOGY
Studies in animals have shown tolmetin sodium to possess anti-inflammatory, analgesic, and antipyretic activity. In the rat, tolmetin prevents the development of experimentally induced polyarthritis and also decreases established inflammation.

The mode of action of tolmetin is not known. However, studies in laboratory animals and man have demonstrated that the anti-inflammatory action of tolmetin is *not* due to pituitary-adrenal stimulation. Tolmetin inhibits prostaglandin synthetase *in vitro* and lowers the plasma level of prostaglandin E in man. This reduction in prostaglandin synthesis may be responsible for the anti-inflammatory action. Tolmetin does not appear to alter the course of the underlying disease in man.

In patients with rheumatoid arthritis and in normal volunteers, tolmetin sodium is rapidly and almost completely absorbed with peak plasma levels being reached within 30-60 minutes after an oral therapeutic dose. In controlled studies, the time to reach peak tolmetin plasma concentration is approximately 20 minutes longer following administration of a 600 mg tablet, compared to an equivalent dose given as 200 mg tablets. The clinical meaningfulness of this finding, if any, is unknown. Tolmetin displays a biphasic elimination from the plasma consisting of a rapid phase with a half-life of one to 2 hours followed by a slower phase with a half-life of about 5 hours. Peak plasma levels of approximately 40 mcg/mL are obtained with a 400 mg oral dose. Essentially all of the administered dose is recovered in the urine in 24 hours either as an inactive oxidative metabolite or as conjugates of tolmetin. An 18-day multiple dose study demonstrated no accumulation of tolmetin when compared with a single dose.

In two fecal blood loss studies of 4 to 6 days duration involving 15 subjects each, tolmetin sodium did not induce an increase in blood loss over that observed during a 4-day drug-free control period. In the same studies, aspirin produced a greater blood loss than occurred during the drug-free control period, and a greater blood loss than occurred during the tolmetin sodium treatment period. In one of the two studies, indomethacin produced a greater fecal blood loss than occurred during the drug-free control period; in the second study, indomethacin did not induce a significant increase in blood loss.

Tolmetin is effective in treating both the acute flares and in the long-term management of the symptoms of rheumatoid arthritis, osteoarthritis and juvenile rheumatoid arthritis.

In patients with either rheumatoid arthritis or osteoarthritis, tolmetin is as effective as aspirin and indomethacin in controlling disease activity, but the frequency of the milder gastrointestinal adverse effects and tinnitus was less than in aspirin-treated patients, and the incidence of central nervous system adverse effects was less than in indomethacin-treated patients.

In patients with juvenile rheumatoid arthritis, tolmetin is as effective as aspirin in controlling disease activity, with a similar incidence of adverse reactions. Mean SGOT values, initially elevated in patients on previous aspirin therapy, remained elevated in the aspirin group and decreased in the tolmetin group.

Tolmetin has produced additional therapeutic benefit when added to a regimen of gold salts and, to a lesser extent, with corticosteroids. Tolmetin should not be used in conjunction with salicylates since greater benefit from the combination is not likely, but the potential for adverse reactions is increased.

INDICATIONS AND USAGE
Tolmetin sodium tablets are indicated for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis. Tolmetin is indicated in the treatment of acute flares and the long-term management of the chronic disease.

Tolmetin is also indicated for treatment of juvenile rheumatoid arthritis. The safety and effectiveness of tolmetin have not been established in children under 2 years of age (see PRECAUTIONS-Pediatric Use and DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS
Anaphylactoid reactions have been reported with tolmetin sodium as with other nonsteroidal anti-inflammatory drugs. Because of the possibility of cross-sensitivity to other nonsteroidal anti-inflammatory drugs, particularly zomepirac sodium, anaphylactoid reactions may be more likely to occur in patients who have exhibited allergic reactions to these compounds. For this reason, tolmetin should not be given to patients in whom aspirin and other nonsteroidal anti-inflammatory drugs induce symptoms of asthma, rhinitis, urticaria or other symptoms of allergic or anaphylactoid reactions. Patients experiencing anaphylactoid reactions on tolmetin should be treated with conventional therapy, such as epinephrine, antihistamines and/or steroids.

WARNINGS
Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy:
Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID (Nonsteroidal Anti-inflammatory Drug) therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAID's even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAID's in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS
General: Because of ocular changes observed in animals and of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop visual disturbances during treatment with tolmetin sodium have ophthalmologic evaluations.

As with other nonsteroidal anti-inflammatory drugs, long-term administration of tolmetin to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

Since tolmetin and its metabolites are eliminated primarily by the kidneys, patients with impaired renal function should be closely monitored, and it should be anticipated that they will require lower doses.

Tolmetin prolongs bleeding time. Patients who may be adversely affected by prolongation of bleeding time should be carefully observed when tolmetin is administered.

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Tolmetin prolongs bleeding time. Patients who may be adversely affected by prolongation of bleeding time should be carefully observed when tolmetin is administered.

In patients receiving concomitant tolmetin-steroid therapy, any reduction in steroid dosage should be gradual to avoid the possible complications of sudden steroid withdrawal.

Peripheral edema has been reported in some patients receiving tolmetin therapy. Therefore, as with other nonsteroidal anti-inflammatory drugs, tolmetin should be used with caution in patients with compromised cardiac function, hypertension, or other conditions predisposing to fluid retention.

The antipyretic and anti-inflammatory activities of the drug may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed non-infectious, non-inflammatory painful conditions. As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with tolmetin. Severe hepatic reactions, including jaundice and fatal hepatitis, have been reported with tolmetin as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), tolmetin should be discontinued.

Information for Patients: Tolmetin, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

NSAID's (Nonsteroidal Anti-Inflammatory Drugs) are often essential agents in the management of arthritis, but they also may be commonly employed for conditions which are less serious.

tolmetin sodium, over 500 of which have undergone [illegible]
body system, are among those typical of nonsteroidal anti-inflammatory drugs and, as expected, gastrointestinal complaints were most frequent. In clinical trials with tolmetin sodium, about 10% of patients dropped out because of adverse reactions, mostly gastrointestinal in nature.

Incidence Greater Than 1%
The following adverse reactions which occurred more frequently than 1 in 100 were reported in controlled clinical trials.

Gastrointestinal: Nausea (11%), dyspepsia,* gastrointestinal distress,* abdominal pain,* diarrhea,* flatulence,* vomiting,* constipation, gastritis, and peptic ulcer. Forty percent of the ulcer patients had a prior history of peptic ulcer disease and/or were receiving concomitant anti-inflammatory drugs including corticosteroids, which are known to produce peptic ulceration.

Body as a Whole: Headache,* asthenia,* chest pain

Cardiovascular: Elevated blood pressure,* edema*

Central Nervous System: Dizziness,* drowsiness, depression

Metabolic/Nutritional: Weight gain,* weight loss*

Dermatologic: Skin irritation

Special Senses: Tinnitus, visual disturbance

Hematologic: Small and transient decreases in hemoglobin and hematocrit not associated with gastrointestinal bleeding have occurred. These are similar to changes reported with other nonsteroidal anti-inflammatory drugs.

Urogenital: Elevated BUN, urinary tract infection

*Reactions occurring in 3% to 9% of patients treated with tolmetin sodium. Reactions occurring in fewer than 3% of the patients are unmarked.

Incidence Less Than 1% (Causal Relationship Probable)
The following adverse reactions were reported less frequently than 1 in 100 in controlled clinical trials or were reported since marketing. The probability exists that there is a causal relationship between tolmetin and these adverse reactions.

Gastrointestinal: Gastrointestinal bleeding with or without evidence of peptic ulcer, perforation, glossitis, stomatitis, hepatitis, liver function abnormalities

Body as a Whole: Anaphylactoid reactions, fever, lymphadenopathy, serum sickness

Hematologic: Hemolytic anemia, thrombocytopenia, granulocytopenia, agranulocytosis

Cardiovascular: Congestive heart failure in patients with marginal cardiac function

Dermatologic: Urticaria, purpura, erythema multiforme, toxic epidermal necrolysis

Urogenital: Hematuria, proteinuria, dysuria, renal failure

Incidence Less Than 1% (Causal Relationship Unknown)
Other adverse reactions were reported less frequently than 1 in 100 in controlled clinical trials or were reported since marketing, but a causal relationship between tolmetin and the reaction could not be determined. These rarely reported reactions are being listed as alerting information for the physician since the possibility of a causal relationship cannot be excluded.

Body as a Whole: Epistaxis

Special Senses: Optic neuropathy, retinal and macular changes

OVERDOSAGE
In the event of overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage followed by the administration of activated charcoal.

DOSAGE AND ADMINISTRATION
In adults with rheumatoid arthritis or osteoarthritis, the recommended starting dose is 400 mg three times daily (1200 mg daily), preferably including a dose on arising and a dose at bedtime. To achieve optimal therapeutic effect the dose should be adjusted according to the patient's response after one or two weeks. Control is usually achieved at doses of 600-1800 mg daily in divided doses (generally t.i.d.). Doses larger than 1800 mg/day have not been studied and are not recommended.

The recommended starting dose for children (2 years and older) is 20 mg/kg/day in divided doses (t.i.d. or q.i.d.). When control has been achieved, the usual dose ranges from 15 to 30 mg/kg/day. Doses higher than 30 mg/kg/day have not been studied and, therefore, are not recommended.

A therapeutic response to tolmetin sodium can be expected in a few days to a week. Progressive improvement can be anticipated during succeeding weeks of therapy. If gastrointestinal symptoms occur, tolmetin can be administered with antacids other than sodium bicarbonate. Tolmetin bioavailability and pharmacokinetics are not significantly affected by acute or chronic administration of magnesium and aluminum hydroxides; however, bioavailability is affected by food (see PRECAUTIONS-Drug-Food Interaction).

HOW SUPPLIED
Tolmetin Sodium Tablets 600 mg - Available in unscored tablets containing tolmetin sodium dihydrate equivalent to 600 mg tolmetin. Each film-coated, orange, oblong tablet is debossed "93" and "214" on one side. Packaged in bottles of 100 and 1000.

Store at controlled room temperature 15°-30°C (59°-86°F).

Protect from light.

Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

CAUTION: Federal law prohibits dispensing without prescription.

Rev. A 4/96

Manufactured by:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

For:
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Sellersville, PA 18960

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAID's may represent an acceptable alternative to both the patient and physician.

Laboratory Tests: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see WARNINGS- Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy).

Drug Interactions: The *in vitro* binding of warfarin to human plasma proteins is unaffected by tolmetin, and tolmetin does not alter the prothrombin time of normal volunteers. However, increased prothrombin time and bleeding have been reported in patients on concomitant tolmetin and warfarin therapy. Therefore, caution should be exercised when administering tolmetin to patients on anticoagulants.

In adult diabetic patients under treatment with either sulfonylureas or insulin there is no change in the clinical effects of either tolmetin or the hypoglycemic agents.

Caution should be used if tolmetin sodium is administered concomitantly with methotrexate. Tolmetin and other nonsteroidal anti-inflammatory drugs have been reported to reduce the tubular secretion of methotrexate in an animal model, possibly enhancing the toxicity of methotrexate.

Drug/Laboratory Test Interactions: The metabolites of tolmetin sodium in urine have been found to give positive tests for proteinuria using tests which rely on acid precipitation as their endpoint (e.g. sulfosalicylic acid). No interference is seen in the tests for proteinuria using dye-impregnated commercially available reagent strips.

Drug-Food Interaction: When tolmetin sodium was taken immediately after a meal, peak plasma tolmetin concentrations were reduced by 50% while total bioavailability was decreased by about 16%.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Tolmetin sodium did not possess any carcinogenic liability in the following long-term studies: a 24-month study in rats at doses as high as 75 mg/kg/day, and an 18-month study in mice at doses as high as 50 mg/kg/day.

No mutagenic potential of tolmetin sodium was found in the Ames Salmonella-Microsomal Activation Test.

Reproductive studies revealed no impairment of fertility in animals. Effects on parturition have been shown, however, as with other prostaglandin inhibitors. This information is detailed in the Pregnancy section below.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Reproduction studies in rats and rabbits at doses up to 50 mg/kg (1.5 times the maximum clinical dose based on a body weight of 60 kg) revealed no evidence of teratogenesis or impaired fertility due to tolmetin. However, tolmetin is an inhibitor of prostaglandin synthetase. Drugs in this class have known effects on the fetal cardiovascular system which may cause constriction of the ductus arteriosus *in utero* during the third trimester of pregnancy, which may result in persistent pulmonary hypertension of the newborn.

There are no adequate and well-controlled studies in pregnant women. Tolmetin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-Teratogenic Effects: Prostaglandin inhibitors have also been shown to increase the incidence of dystocia and delayed parturition in animals.

Nursing Mothers: Tolmetin has been shown to be secreted in human milk. Because of the possible adverse effects of prostaglandin inhibiting drugs on neonates, use in nursing mothers should be avoided.

Pediatric Use: The safety and effectiveness of tolmetin sodium for pediatric patients under 2 years of age have not been established.

ADVERSE REACTIONS

The adverse reactions which have been observed in clinical trials encompass observations in about 4370 patients treated with tolmetin sodium, over 800 of whom have undergone at least one year of therapy. These adverse reactions, reported below by body system, are among those typical of nonsteroidal anti-inflammatory drugs and, as expected, gastrointestinal complaints were most frequent. In clinical trials with tolmetin sodium, about 10% of patients dropped out because of adverse reactions, mostly gastrointestinal in nature.

Incidence Greater Than 1%

The following adverse reactions which occurred more frequently than 1 in 100 were reported in controlled clinical trials.

Gastrointestinal: Nausea (11%), dyspepsia,* gastrointestinal distress,* abdominal pain,* diarrhea,* flatulence,* vomiting,* constipation, gastritis, and peptic ulcer. Forty percent of the ulcer patients had a prior history of peptic ulcer disease and/or were receiving concomitant anti-inflammatory drugs including corticosteroids, which are known to produce peptic ulceration.

Body as a Whole: Headache,* asthenia,* chest pain

Cardiovascular: Elevated blood pressure,* edema*

Central Nervous System: Dizziness,* drowsiness, depression

Metabolic/Nutritional: Weight gain,* weight loss*

Dermatologic: Skin irritation

Special Senses: Tinnitus, visual disturbance

Hematologic: Small and transient decreases in hemoglobin and hematocrit not associated with gastrointestinal bleeding have occurred. These are similar to changes reported with other nonsteroidal anti-inflammatory drugs.

Urogenital: Elevated BUN, urinary tract infection

*Reactions occurring in 3% to 9% of patients treated with tolmetin sodium. Reactions occurring in fewer than 3% of the patients are unmarked.

Incidence Less Than 1% (Causal Relationship Probable)

The following adverse reactions were reported less frequently than 1 in 100 in controlled clinical trials or were reported since marketing. The probability exists that there is a causal relationship between tolmetin and these adverse reactions.

Gastrointestinal: Gastrointestinal bleeding with or without evidence of peptic ulcer, perforation, glossitis, stomatitis, hepatitis, liver function abnormalities

Body as a Whole: Anaphylactoid reactions, fever, lymphadenopathy, serum sickness

Hematologic: Hemolytic anemia, thrombocytopenia, granulocytopenia, agranulocytosis

Cardiovascular: Congestive heart failure in patients with marginal cardiac function

Dermatologic: Urticaria, purpura, erythema multiforme, toxic epidermal necrolysis

Urogenital: Hematuria, proteinuria, dysuria, renal failure

Incidence Less Than 1% (Causal Relationship Unknown)

Other adverse reactions were reported less frequently than 1 in 100 in controlled clinical trials or were reported since marketing, but a causal relationship between tolmetin and the reaction could not be determined. These rarely reported reactions are being listed as alerting information for the physician since the possibility of a causal relationship cannot be excluded.

Body as a Whole: Epistaxis

Special Senses: Optic neuropathy, retinal and macular changes

OVERDOSAGE

In the event of overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage followed by the administration of activated charcoal.

DOSAGE AND ADMINISTRATION

In adults with rheumatoid arthritis or osteoarthritis, the recommended starting dose is 400 mg three times daily (1200 mg daily), preferably including a dose on arising and a dose at bedtime. To achieve optimal therapeutic effect the dose should be adjusted according to the patient's response after one or two weeks. Control is usually achieved at doses of 600-1800 mg daily in divided doses (generally t.i.d.). Doses larger than 1800 mg/day have not been studied and are not recommended.

The recommended starting dose for children (2 years and older) is 20 mg/kg/day in divided doses (t.i.d. or q.i.d.). When control has been achieved, the usual dose ranges from 15 to 30 mg/kg/day. Doses higher than 30 mg/kg/day have not been studied and, therefore, are not recommended.

A therapeutic response to tolmetin sodium can be expected in a few days to a week. Progressive improvement can be anticipated during succeeding weeks of therapy. If gastrointestinal symptoms occur, tolmetin can be administered with antacids other than sodium bicarbonate. Tolmetin bioavailability and pharmacokinetics are not significantly affected by acute or chronic administration of magnesium and aluminum hydroxides; however, bioavailability is affected by food (see PRECAUTIONS- Drug-Food Interaction).

HOW SUPPLIED

Tolmetin Sodium Tablets 600 mg - Available in unscored tablets containing tolmetin sodium dihydrate equivalent to 600 mg tolmetin. Each film-coated, orange, oblong tablet is debossed "93" and "214" on one side. Packaged in bottles of 100 and 1000.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074729

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3 2. ANDA # 74-729

3. NAMES AND ADDRESSES
Lemmon Company
Attention: Deborah A. Jaskot
650 Cathill Road, Sellersville, PA 18960

Manufacturer: TEVA Pharmaceutical Industries Ltd.
P.O. Box 353 KFAR SABA 44102 Israel

4. LEGAL BASIS FOR SUBMISSION Tolectin® 600

5. SUPPLEMENTS N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME **Tolmetin Sodium Tablets, USP**

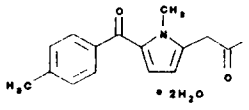
8. SUPPLEMENTS PROVIDE FOR: N/A

9. AMENDMENTS AND OTHER DATES:

01-05-97	Facsimile Amendment- **this review**
01-08-97	Chemistry Minor Letter Out
08-29-96	Labeling Review-approve
08-02-96	Major Amendment
08-11-95	Original Submission

10. PHARMACOLOGICAL CATEGORY NSAID 11. Rx

12. RELATED IND/NDA/DMFs



13. DOSAGE FORM tablet, oral

14. POTENCY **600 mg**, capsule shape, beveled edges, film coated tablet embossed with the numbers 93/214 on one side and plain on the other

15. CHEMICAL NAME AND STRUCTURE
$C_{15}H_{14}NNaO_3.2H_2O$; M.W. = 315.30 CAS [64490-92-2]
Sodium 1-methyl-5-*p*-toluoylpyrrole-2-acetatedihydrate

16. RECORDS AND REPORTS N/A

17. COMMENTS none

18. CONCLUSIONS AND RECOMMENDATIONS: **APPROVE**

19. REVIEWER: Melissa Maust DATE COMPLETED: February 12, 1997
cc: ANDA 74-729
Division File
Endorsements:
HFD-623/M.Maust 2-12-97 2/14/97
HFD-623/V. Sayeed, Ph.D./
Y:\NEW\FIRMSAM\LEMMON\LTRS&REV\74729R3.AP
F/T by:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074729

BIOEQUIVALENCE REVIEWS

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-729 SPONSOR: Lemmon Company
DRUG: Tolmetin Sodium
DOSAGE FORM: Tablets
STRENGTH(s): 600 mg
TYPE OF STUDY: Single/~~Multiple~~ Fasting/Fed
STUDY SITE:

STUDY SUMMARY: The bioequivalence Studies under fasting and non fasting conditions conducted on Tolmetin Sodium, 600 mg Tablets are acceptable.

DISSOLUTION: The dissolution testing is acceptable.

PRIMARY REVIEWER: BRANCH: III
INITIAL: DATE: 1/11/96

BRANCH CHIEF: BRANCH:
INITIAL: DATE: 1/14/96

DIRECTOR
DIVISION OF BIOEQUIVALENCE
INITIAL: DATE: 1/31/96

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL: N/A DATE:

DIV

ANDA 74-729

JAN 30 1996

Lemmon Company
Attention: Deborah Jaskot
650 Cathill Road
Sellersville PA 18960

Dear Madam:

Reference is made to your abbreviated new drug application dated August 11, 1995, submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Tolmetin Sodium Tablets USP, 600 mg.

The following comments pertain **only** to bioequivalency issues in the August 11, 1995 submission.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in **900 mL of solutions A&B, pH 4.5 at 37°C using USP 23 apparatus II at 50 rpm**. The test product should meet the following specifications:

   Not less than of the labeled amount of the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JAN 18 1996 D,C

Tolmetin Sodium
600 mg Tablets
ANDA # 74-729
Reviewer: Moheb H. Makary
WP 74729SD.895

Lemmon Company
Sellersville, PA
Submission Date:
August 11, 1995

Review of Bioequivalence Studies and Dissolution Data

I. Objective:

The firm has submitted two bioequivalence studies under fasting and nonfasting conditions for its 600 mg Tolmetin sodium Tablets and dissolution data to compare the test product relative to Tolectin^R 600 mg Tablets for review.

II. Introduction:

Tolmetin sodium is nonsteroidal anti-inflammatory agent which is freely soluble in water. Its mode of action is unknown. The drug is rapidly and almost completely absorbed following oral dosing with peak plasma levels being reached in about 30-60 minutes. Tolmetin displays a biphasic elimination from plasma consisting of rapid phase (T1/2 = 1-2 hours) followed by slower phase (T1/2 = 5 hours). Peak plasma levels of about 40-50 ug/mL are obtained with 400 mg oral dose. Decreases in the rate and extent of drug absorption have been reported for tolmetin when dosed immediately after a meal. Peak plasma tolmetin concentrations were reduced by 50% while total bioavailability was decreased by 16%.

Essentially all of the dose is recovered in the urine within 24 hours either as an inactive metabolite or as conjugates of tolmetin. Tolmetin sodium is available as 400 mg oral capsules and as 200 mg and 600 mg oral tablets, manufactured by McNeil Pharmaceuticals Inc.

III. Study #Lemmon/Teva B-06282 For Single-Dose, Two-Way Crossover Of Tolmetin Sodium Tablet, 600 mg, Under Fasting Conditions:

The objective of the study was to compare the bioavailability of Tolmetin Sodium Tablets, 600 mg, manufactured by Lemmon Company, with that of McNeil Pharmaceuticals Inc., product (Tolectin^R), following an oral administration of a single 600 mg dose (1x600 mg tablet) of each product under fasting conditions.

Clinical site:

Analytical site:

Sponsor:	Lemmon Company Sellersville, PA.
Study design:	A single-dose, randomized, two-treatment, two-period, two-sequence crossover design.
Subjects:	Thirty-eight healthy male volunteers were enrolled in the study. Thirty-eight subjects were dosed period I, and all 38 subjects successfully completed the entire clinical portion of the study.
Selection criteria:	Selection criteria include male volunteers between the age of 18 and 41 years with physical examination and medical history within normal limits, body weight within ± 10% of ideal body weight (Metropolitan Life Insurance Bulletin, 1983), and normal electrocardiogram. Physical exam, ECG and laboratory tests were conducted within 2 weeks of the study.
Laboratory tests:	Blood chemistry, urine analysis, liver and kidney function tests were performed within 2 weeks of the study. Laboratory evaluations were not exceeded 10% of normal limits.
Exclusion criteria:	Exclusion criteria were: ingestion of an investigational drug within four weeks prior to entry into the study; smoking tobacco; an acute illness or surgery during the four weeks prior to entry into the study; history of adverse reactions or allergy to aspirin, tolmetin or the nonsteroidal drugs; presence of significant renal, cardiac, hematopoietic, neurological, pulmonary or gastrointestinal pathology; presence of psychiatric disorders, glaucoma, diabetes or hyperthyroidism; any medications (including OTC) within fourteen days prior to the start of the study; ingestion of alcoholic beverage or caffeine or xanthine-containing food or beverages within 72 hours prior to start of the study.
Dose and treatment:	All subjects completed an overnight fast (10 hours) before any of the following drug treatments: (a) Test product: A: 1x600 mg Tolmetin Sodium Tablet (Lemmon Company), lot # K-18052, lot size tablets, content uniformity 100.1% (1.56% CV)

and potency 99.1%.

(b) Reference product:

B: 1x600 mg Tolectin^{R} Tablet (McNeil Labs, Inc.), lot # LA3809P, Exp. 1/96, content uniformity 98.5% (1.52% CV) and potency 99.2%.

Food and fluid intake: A 600 mg (1 Tablet) tolmetin sodium of either the test or reference product was administered with 240 mL of water. Lunch was served 4 after dosing.

Washout period: One week

Blood samples: 10 mL blood samples were collected at 0 (pre-dose), 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours. Plasma samples were immediately stored at -20^{o}C until analyzed.

Statistical Analysis:

Statistical analysis was performed using SAS PROC GLM procedure. Noncompartmental pharmacokinetic parameters were evaluated by ANOVA. A separate analysis of variance was performed for the natural log transformed pharmacokinetic parameters AUCL, AUCi and Cmax.

V. In Vivo Results:

Thirty-eight healthy male subjects were entered into the study. The study was successfully completed in all 38 subjects enrolled. Ten adverse events were reported in seven of thirty-eight subjects dosed over the course of the study. The adverse events were headache, myalgia, pharyngitis and respiratory disorder. Only two events were considered to be probably related to the study drug. None of the adverse events resulted in dropping any subject from the study nor were they considered serious. There were twelve minor deviations from the protocol restriction of no prescription or non-prescription medications within fourteen days of period I. The reported medications were not suspected to interfere with the integrity of the study. In general, all blood collection were successfully completed as per protocol design.

The plasma tolmetin concentrations and pharmacokinetic parameters are summarized in Table I below:

Table I

Mean Plasma Tolmetin Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 600 mg Tolmetin Sodium (1X600 mg Tablet) Under Fasting Conditions
(N=38)

Time hr	Lemmon Test Product Lot # K-18052 ug/mL (CV)	McNeil Reference Product Lot # LA3809P ug/mL (CV)
0	0	0
0.17	5.95 (202.8)	3.99 (217.7)
0.33	35.34 (88.59)	24.15 (121.4)
0.5	44.01 (62.03)	33.96 (79.33)
0.75	35.77 (54.13)	39.39 (50.58)
1	28.21 (53.84)	32.93 (43.52)
1.25	23.88 (53.86)	26.14 (46.70)
1.5	20.63 (60.32)	20.89 (49.53)
2	15.08 (73.31)	15.13 (51.39)
3	11.20 (83.95)	9.12 (73.10)
4	6.48 (84.96)	6.41 (86.68)
6	2.25 (90.78)	2.28 (83.43)
8	0.91 (90.87)	0.93 (80.04)
10	0.47 (89.40)	0.47 (87.59)
12	0.29 (121.5)	0.28 (101.3)
16	0.03 (472.9)	0.02 (430.3)
24	0	0

Pharmacokinetic Parameters:

	Test	Reference	90% CI Log
AUCL (ug.hr/mL)	85.62 (40.8)	81.87 (33.9)	97.6-109.0
AUCi (ug.hr/mL)	86.82 (40.7)	83.19 (33.6)	97.4-108.7
Cmax (ug/mL)	57.47 (34.3)	53.12 (39.7)	99.0-125.4
Kel(1/hr)	0.36	0.36	
HALF(hr)	2.11	2.25	
TMAX (hr)	0.799	0.850	

1. The plasma tolmetin levels peaked at 0.5 and 0.75 hour for the test and reference products, respectively. The plasma levels were comparable for the test and reference products. There were no statistically significant differences between the plasma tolmetin

levels at all sampling time points except at 0.17 and 0.5 hour.

2. For Lemmon's test product the mean AUCL, AUCi and Cmax were 4.6%, 4.4% and 8.2% higher, respectively, than those of the reference product values under fasting conditions. The 90% confidence intervals for the log-transformed parameters were within the acceptable ranges of 80-125% for AUCL and AUCi, and 80-130% for Cmax (Division's memo dated September 11, 1990). The reviewer's calculations were in agreement with those submitted by the firm.

3. Analysis of variance (ANOVA) detected a significant period effects for AUCL and AUCI which has no effect on the outcome of the study.

VI. Study #Lemmon/Teva B-07012 For Single Dose Post-Prandial Bioequivalence Study

The objective of the study is to compare the relative bioavailability of tolmetin sodium 600 mg tablets (Lemmon Company) with that of Tolectin^{R} 600 mg tablets (McNeil) in healthy male volunteers under-nonfasting conditions, and to compare the difference in plasma levels after dosing with the test product when dosed with and without food.

Clinical site:

Analytical site:

Study design:	A single-dose, randomized, three-treatment, six-sequence, three-period crossover design.
Subjects:	Eighteen (18) healthy male volunteers were enrolled in the study. Subject #6 dropped from the study prior to period II dosing secondary to a family emergency. Seventeen (17) subjects successfully completed the entire clinical portion of the study.
Selection criteria:	Same as study #B-06282 above.
Washout period:	One week
Dose and treatment:	Treatment A: 1x600 mg Tolmetin Sodium Tablet (Lemmon), lot #K-18052 administered following an overnight fast. Treatment B: 1x600 mg Tolmetin Tablet (Lemmon), lot #K-18052, administered after a high fat breakfast preceded by an overnight fast.

Treatment C:
1x600 mg Tolectin® Tablet (McNeil), lot #LA3809P administered after a high fat breakfast preceded by an overnight fast.

Food and fluid intake: Subjects were required to fast overnight for 10 hours prior to dosing in each treatment phase. Subjects on regimen A ingested the tablet with 240 mL of water. Subjects on regimen B and C ingested the tablet with 240 mL of water within 30 minutes after a standardized high-fat breakfast (1 fried egg, 1 serving of hashed browned potatoes, 1 slice Canadian bacon, 1 buttered English muffin, 1 slice American cheese, 8 ounces of whole milk and 6 ounces of orange juice). Lunch was served at 4 hours post-dose. Liquids were ad libitum after lunch.

Blood samples: Same as study #B-06282 above.

Assay Methodology: Same as study #B-06282 above.

Statistical Analysis:

Statistical analysis was performed using SAS PROC GLM procedure. Noncompartmental pharmacokinetic parameters were evaluated by ANOVA.

VII. In Vivo Results:

Eighteen (18) healthy male subjects were dosed period I of the study, and seventeen (17) subjects finished the entire clinical portion of the study.
Sixteen adverse events were reported in seven of eighteen subjects dosed over the course of the study. The adverse events were headache, abdominal pain, coughing, nausea, pharyngitis, rhinitis and vomiting. Only six events were considered to be probably related to the study drug. None of the adverse events resulted in dropping any subject from the study nor were they considered serious. There were five minor deviations from the protocol restriction of no prescription or non-prescription medications within fourteen days of period I. The reported medications were not suspected to interfere with the integrity of the study. In general, all blood collection were successfully completed as per protocol design.

The plasma tolmetin concentrations and pharmacokinetic parameters are summarized in Table II below:

Table II

Mean Plasma Tolmetin Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 600 mg Tolmetin Sodium (1X600 mg Tablet) Under Fasting and Nonfastin Conditions
(N=17)

Time hr	Lemmon Test Product Lot #K-18052 Fasting ug/mL (CV)	Lemmon Test Product Lot # K-18052 Nonfasting ug/mL (CV)	McNeil Reference Product Lot # LA3809P Nonfasting ug/mL (CV)
0	0	0	0
0.17	8.76 (137.7)	0.14 (214.3)	0.01 (165.1)
0.33	34.51 (85.3)	1.24 (168.8)	1.21 (159.3)
0.5	45.87 (50.0)	3.67 (225.1)	3.32 (148.8)
0.75	37.61 (59.0)	5.40 (184.0)	8.06 (112.3)
1	28.52 (54.3)	7.06 (131.5)	12.60 (92.1)
1.25	22.98 (46.7)	10.00 (104.4)	17.84 (72.2)
1.5	19.17 (44.8)	11.60 (79.1)	21.36 (57.0)
2	15.24 (47.9)	12.55 (64.9)	17.26 (46.0)
3	10.71 (76.5)	12.86 (50.2)	11.25 (38.2)
4	6.42 (81.2)	11.00 (56.6)	7.90 (48.5)
6	2.20 (65.7)	4.09 (55.2)	3.00 (57.1)
8	0.82 (38.1)	1.29 (44.3)	1.03 (50.9)
10	0.43 (49.8)	0.65 (49.2)	0.51 (56.5)
12	0.21 (106.1)	0.43 (45.5)	0.25 (94.4)
16	0.02 (412.3)	0.16 (170.4)	0.08 (288.7)
24	0	1.10 (285.9)	0.42 (366.1)

Pharmacokinetic Parameters:

	A Test Fasting	B Test Nonfasting	C Reference Nonfasting	B/C
AUCL (ug.hr/mL)	85.02 (22.4)	63.24 (32.1)	64.31 (28.7)	0.98
AUCi (ug.hr/mL)	86.37 (22.1)	64.97 (30.6)	65.96 (28.3)	0.98
Cmax (ug/mL)	56.16 (31.5)	20.62 (50.8)	25.50 (44.7)	0.81
Kel(1/hr)	0.332	0.29	0.36 (46.8)	
HALF(hr)	2.44	3.24	2.78	
TMAX (hr)	0.792	2.59	1.83	

1. The plasma tolmetin levels peaked at 3 and 1.5 hours for the test and reference products, respectively, under nonfasting conditions. There were no statistically significant differences between the plasma tolmetin levels at all sampling time points except at 1.25, 1.5, 2 and 12 hours, under nonfasting conditions.

2. For Lemmon's test product the mean AUCL, AUCi and Cmax were 1.7%, 1.5% and 19.1% lower, respectively, than those of the reference product values under nonfasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUC(0-t), AUCinf and Cmax. The reviewer's calculations were in agreement with those submitted by the firm.

3. The means AUCL, AUCi and Cmax of the test product were reduced by 25.6%, 24.8% and 63.3%, respectively, when dosed under nonfasting conditions compared to fasting conditions. These reduction in values of AUC and Cmax are in agreement with reference product's labeling which indicates a 16% drop in bioavailability and a 50% drop in Cmax in a single dose study under nonfasting versus fasting conditions.

4. Subject #13, the concentration value at 24 hours for dosing period I was 0.404 ug/mL. This value came after values of 0.294 ug/mL at 12 hours and 0 ug/mL at 16 hours. This unusual value occurred during the period where the subject dosed with the reference product after a high fat breakfast. The 24 hour plasma concentration was not used for the AUCL and a AUCi calculations, and was not used in determining the values for Kel and HALF.

5. Subject #14 had unusually high plasma tolmetin concentrations for dosing periods II and III at 24 hours. For period II, where the subject was dosed with the reference product after a high fat breakfast, the plasma tolmetin concentrations were 0.258 ug/mL at 10 hours, 0.0 ug/mL at 12 and 16 hours, and 6.42 ug/mL at 24 hours. This value was not used in the AUCL, AUCi, Kel and HALF calculations. Also, for this case, the 24 hour concentration would have been Cmax and 24 hours the Tmax value.
The concentrations for period III, where the subject was dosed with the test product after a high fat breakfast, were similar to those seen for period II except that the 24 hour plasma tolmetin concentration of 6.98 ug/mL was not the Cmax. This value was not used in the AUCL, AUCi, Kel and HALf calculations.

6. Subject #17 had a very unusually high plasma tolmetin concentration at 24 hours for the period II dosing, where the subject was dosed with the test product after a high fat breakfast. The plasma tolmetin concentrations were 0.672 ug/mL at 10 hours, 0.468 ug/mL at 12, 0.344 ug/mL at 16 hours, and 11.4 ug/mL at 24 hours. Here, as above, the 24 hour value was not used for the AUCL, AUCi, Kel and Half calculations. This value at 24 hours also represent the Cmax and 24 hours the Tmax.

7. Whether to use, or not use, of these values for Cmax comparisons (subjects #14 & 17) is a difficult issue. These

values were not used in the main comparisons presented in this report. However, using these values for Cmax in the statistical analysis, the results were only slightly different. The outcome of the study was not different either way (i.e., the ratio of the test mean to the reference mean remains within the acceptable range of 0.8-1.2 for Cmax).

8. Subject #7 experienced a mild episode of vomiting for the period I dosing, where the subject was dosed with the test product after a high fat breakfast. Since the vomiting episode occurred after 12 hours of dosing, including the subject in the statistical analysis should not affect the outcome of the study.

VIII. Product Formulation:

Lemmon's formulation for its Tolmetin Sodium 600 mg tablet is shown below:

Tolmetin Sodium Tablet 600 mg

Ingredients	Amount/Tablet
Tolmetin Sodium USP Dihydrate	735.0 mg*
Starch NF	
Purified Water USP	
Crospovidone NF	
Colloidal Silicon Dioxide NF	
Microcrystalline Cellulose NF	
Magnesium Stearate NF	
Coating	
(Orange)	
Polyethylene Glycol 400 NF	
Purified Water USP	
Total	997.0 mg

* Equivalent to 600.0 mg Tolmetin

IX. In Vitro Dissolution Testing:

Method:	USP 23 apparatus II (paddle), at 50 rpm
Medium:	900 mL of phosphate buffer, pH 4.5
Number of Capsules:	12
Test product:	Lemmon's Tolmetin Sodium 600 mg Table, lot # K-18052
Reference product:	McNeil's Tolectin^R 600 mg Tablet, lot #LA3809P
Specification:	NLT in 30 minutes

Dissolution testing results are presented in Table III.

X. Comments:

1. The firm's in vivo bioequivalence study under fasting conditions, conducted on its 600 mg tolmetin sodium Tablet is acceptable. The confidence intervals for AUCL, AUCi and Cmax are within the acceptable range of 80-125% for AUC and 80-130% for Cmax.

2. The firm's in vivo single-dose bioequivalence study under nonfasting conditions is acceptable. The ratios of the test mean to the reference mean were within the acceptable range of 0.80-1.20 for AUCL, AUCi and Cmax.

6. The in vitro dissolution testing for the test product 600 mg tolmetin sodium tablet is acceptable.

X. Recommendations:

1. The bioequivalence studies conducted by Lemmon Company under fasting and nonfasting conditions on its tolmetin sodium, 600 mg Tablet, lot #K-18052, comparing it to McNeil's Tolectin^R 600 mg Tablet have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Lemmon's tolmetin sodium tablet, 600 mg is bioequivalent to the reference product, Tolectin^R, 600 mg tablet, manufactured by McNeil Pharmaceutical.

2. The dissolution testing conducted by Lemmon Company on its tolmetin sodium, 600 mg Tablet, lot #K-18052 is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of solutions A&B, pH 4.5 at 37 °C using USP 23 apparatus II at 50 rpm. The test product should meet the following specifications:

phosphate buffer

Not less than of the labeled amount of the dosage form is dissolved in 30 minutes.

K

1/18/96

The firm should be informed of the above recommendations.

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATR _____ Date: 1/12/96

Concur: _____ Date: 1/18/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

MMakary/1-11-96 wp 74729SD.895
cc: ANDA #74-729, original, HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-658 (Mhatre, Makary), Drug File, Division File.

Table III. In Vitro Dissolution Testing

Drug (Generic Name): Tolmetin Sodium
Dose Strength: 600 mg Tablet
ANDA No.: 74-729
Firm: Lemmon Company
Submission Date: August 11, 1995
File Name: 74729SD.895

I. Conditions for Dissolution Testing:

USP XXII Basket: No. Paddle: X RPM: 50
Units Tested: 12
Medium: 900 mL of phosphate buffer, pH 4.5
Specifications: NLT in 30 minutes
Reference Drug: McNeil's Tolectin
Assay Methodology

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # K-18052 Strength(mg) 600			Reference Product Lot # LA3809P Strength(mg) 600		
	Mean %	Range	%CV	Mean %	Range	%CV
10	67.7		20.3	57.8		13.2
20	99.3		1.2	97.7		1.8
30	100.1		1.9	100.1		3.4

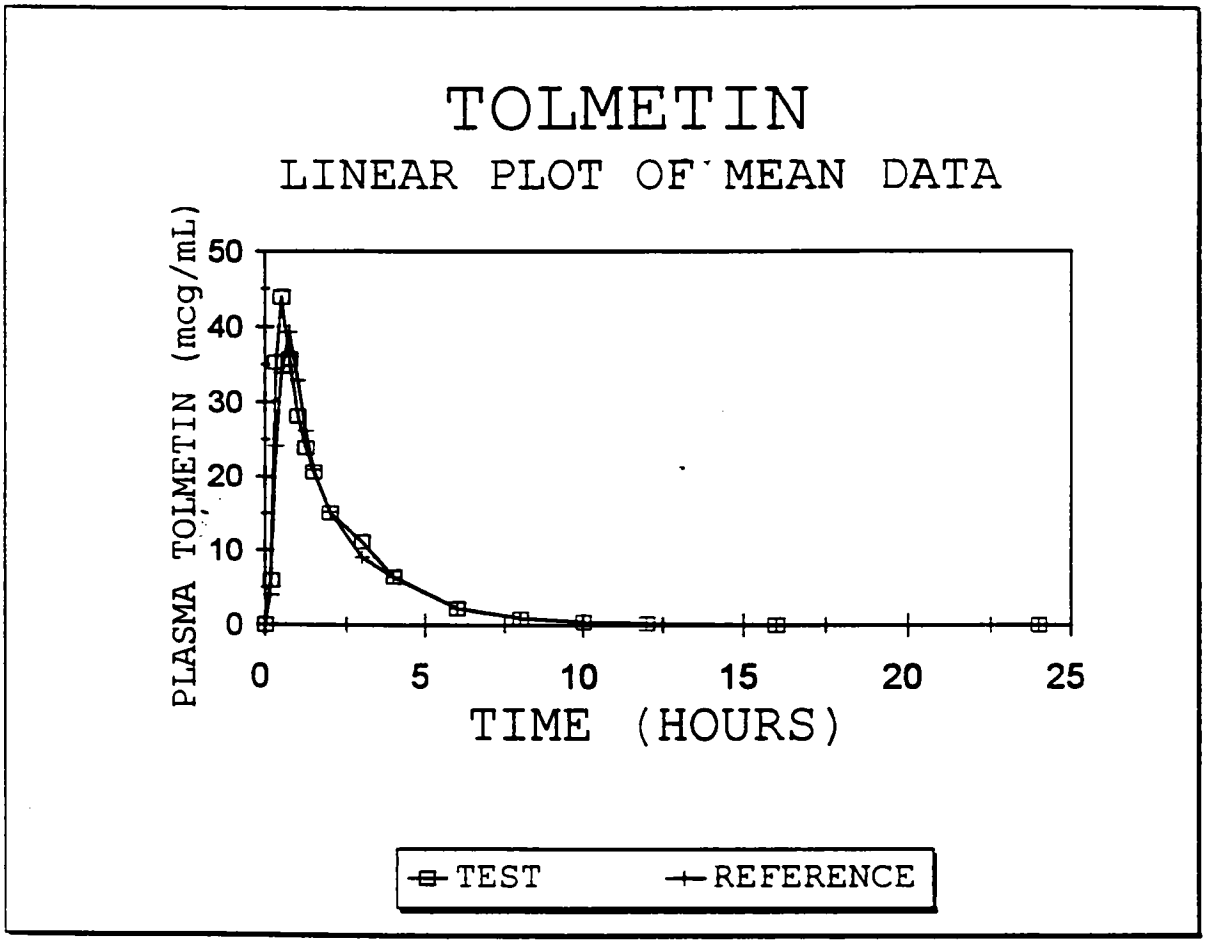

TOLMETIN
LINEAR PLOT OF MEAN DATA
PLASMA TOLMETIN (mcg/mL)
50
40
30
20
10
0
0
5
10
15
20
25
TIME (HOURS)
TEST
REFERENCE

Figure 4.5.1 Linear Plot of Mean Plasma Tolmetin Concentrations *vs* Time